

A DISCOURSE
ON
EHRlich's "CHEMOTHERAPY,"

AND ON CERTAIN GENERAL PRINCIPLES WHICH
REQUIRE TO BE BROUGHT INTO APPLICATION
IN ALL TREATMENT OF BACTERIAL DISEASE.

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EHRlich, who was the originator of the therapeutic method which is to supply a principal theme of this discourse, elected to call this method of his devising—chemotherapy. That appellation must be judged unfortunate. For it runs counter to all principles of sound nomenclature to transfer to a species an appellation which properly belongs to a genus (and the name chemotherapy belongs, of course, by right, to every form of chemical treatment). A delinquency in nomenclature such as this can be retrieved only by adding to the appellation given a full complement of defining and interpreting clauses.

Here the following complement of glosses must be supplied:—

1. Chemotherapy, in Ehrlich's sense, signifies aggressive chemical action exerted on a biological element which is parasitic upon the organism. In other words, chemotherapy, in Ehrlich's sense, means for all ordinary purposes: *specific parasitocidal chemotherapy*.

2. Further, chemotherapy, as understood by Ehrlich, signifies chemical action, which, while attacking parasitic elements, leaves the organism fundamentally unaffected. (In other words, chemotherapy, in Ehrlich's sense, would, expressed in his terminology, be: *specific parasitocidal, predominantly monotropic chemotherapy*).

3. Lastly, the chemotherapy Ehrlich had in view was treatment by artificially manufactured chemical products, as distinguished from products elaborated in the animal organism in response to infection or vaccination. In conformity with this, Ehrlich's chemotherapy would be properly described as: *specific parasitocidal, predominantly monotropic pharmacotherapy*. Let me, in the sequel, use the term *pharmacotherapy* where Ehrlich would have spoken of *chemotherapy*.

We may now turn from the definition of the method to the conceptions which gave it birth. The fundamental principle of pharmacotherapy is that expressed in Ehrlich's dictum: that every substance which exerts any chemical action upon a body cell or tissue, or parasitic organism, does so by virtue of its anchoring itself—i.e., by laying chemical hold upon the

element in question. That is the doctrine incorporated in Ehrlich's formula: *corpora non agunt nisi fixata*. The accessory ideas which afterwards grouped themselves round this foundational axiom were propounded by their author through the vehicle of technical terms. In choosing technical terms as the vehicle for his ideas, Ehrlich was, as reflection will show us, acting under happy inspiration. Let us, in this connexion, note that it has been pregnantly said of words in general—and this holds in a very special sense of technical terms—that they are in reality “agents of universal instruction.” Further, words of all kinds, and “terms of art” more than all, furnish a *memoria technica*—one which keeps in mind things that would, if the words were not there to retain them, escape from the memory. The Latin apophthegm recounts it well: *Nomina si nescis, perit et cognitio rerum*.

In view of what has just been said, it will be seen that we may fittingly begin by studying the vocabulary in which Ehrlich has given expression to his conceptions on pharmacotherapy. In setting out that terminology it will be convenient to place in each case, the one over against the other, those terms that are antonyms, and to print in italics such words that are either lacking in precision or would be prone to carry into the mind erroneous implications.

EHRLICH'S APPARATUS OF TECHNICAL TERMS.

Receptor.	Haptophore (Hapten).
Mono-tropic.	Poly-tropic.
<i>Organo-tropic</i> .	<i>Parasito-tropic</i> .
(For example: neuro- hæmato- leucocyto- and erythrocyto- tropic.)	(For example: bacterio- staphylo- pneumo- or try- panosomato- tropic.)
<i>Dosis Tolerata</i> .	<i>Dosis Efficax</i> .
Therapia magna sterilisans.	<i>Therapia sterilisans fractionata</i> .
Cribrum therapeuticum.	

We may now, though this will involve rehearsing some very familiar material, proceed to pass in review this syllabus of technical terms. The expression *receptor*, as employed by Ehrlich, designates the atomic group in the body cell, tissue, or parasitic organism upon which the chemical agent in question anchors itself. The expression *haptophore* (which is the antonym to receptor) denotes the atomic group by which the chemical agent in question anchors itself to (the Greek says *grasps*) the receptor. The suffix *-tropic* applied to a chemical agent indicates that the substance in question combines with (the Greek says *turns toward*) the kind of cell, tissue, or parasite which is designated by the verbal stem to which the suffix is articulated. The classification into *parasito-* and *organo-* (or as we might better say instead of *organo-*, *histo-*) *tropic* is prone to mislead, inasmuch as it might erroneously suggest to the

mind that the chemical affinities here in question are mutually exclusive, and that a chemical agent which is *parasito-tropic* cannot at one and the same time be *organo-tropic*. This particular blemish may, however, be deemed retrieved by Ehrlich having taken up into his vocabulary the expressions *mono-* and *poly-tropic* (these were coined by me in the mould supplied by Ehrlich), which definitely enunciate that an agent may combine either exclusively with one kind of cell, tissue, or parasitic organism, or, as the case may be, with a number of different kinds of cells, tissues, parasitic organisms, or any combination of these. But what we really require to know about a *polytropic* drug (and practically all drugs are *polytropic*) is whether it combines preferentially with, let us say, the parasitic element, and, *faute de mieux*, with the tissues and cells of the host; or, vice versa, preferentially with the cells and tissues of the body and only *faute de mieux* with the parasite. This might perhaps be conveniently expressed by saying that what we want to know of a drug is whether it is *proterotropic* for the parasite and *hysterotropic* for cells and tissues of the body, or whether it is *proterotropic* for the host and *hysterotropic* for the parasitic organism.

Following on now in our table we come to the expressions *dosis tolerata* and *dosis efficax*. Upon the accurate determination of these a very great deal depends. For the doctrine of Ehrlich tells us that the value of a therapeutic agent depends upon the *dosis tolerata* being definitely larger than the *dosis efficax*. And that doctrine is clearly empty of content if in this therapeutic fractional coefficient $\left(\frac{\textit{dosis tolerata}}{\textit{dosis efficax}}\right)$ the terms which serve as numerator and denominator, are ambiguous. And *de facto* that is the position of things. That the term a *dosis tolerata* is a term of ambiguous meaning will be obvious when we consider that a *dosis tolerata* might mean on the one hand a dose which is *tolerated by the organism taken as a whole*, and on the other hand a dose which is *tolerated by the leucocytes*—those cellular elements which the drug entering the blood first encounters. Ehrlich, when he used the term, had in view, of course, the dose *tolerated by the body as a whole*. Further, he had in view not the, presumably smaller, quantum that can be administered to the diseased, but that, presumably larger, quantum which can be given to healthy men or animals without killing or manifestly poisoning them. But a clinically tolerated dose as thus defined is in point of fact in many cases a dose which weakens or abolishes the antibacterial defence of the body by poisoning the leucocytes. Such a quantum is obviously quite improperly designated a *dosis tolerata*. It would be much better called either a *dosis inermans* (i.e., a disarming dose) or a *dosis destituens* (a dose which leaves the body destitute of leucocytic defence).

The practical importance of the distinction between that (generally larger) quantum of a chemical agent which can be clinically tolerated and that (generally smaller) quantum which can be tolerated by the leucocytes is of obvious practical significance. It is common sense that a quantum of a chemical agent which paralyses the leucocytic defence must when administered to an animal organism which is suffering from a bacterial infection or which is (I am thinking here of prophylactic inoculation) to be exposed to risk of such infection, must work for mischief.

We turn now to the consideration of the term *dosis efficax*. A moment's consideration will show that this expression also is ambiguous. It may mean, to begin with, either a *dosis omnino sterilisans* (such a dose as would sterilise the entire body), or (and this would be the ordinary meaning of the term) a *dosis sanguini-sterilisans* (a quantum that would sterilise the blood). And again the term *dosis efficax* might mean a *dosis uno ictu efficax*, or a *dosis sæpius repetenda*. Or, finally, it might mean the grand total dose of the drug which is, given in divided doses, required for the achievement of a satisfactory result.

This brings us to the consideration of Ehrlich's therapeutic projects. The first of these, the *therapia magna sterilisans*—i.e., the project of sterilising the whole body by a *dosis uno ictu efficax*—that is sterilising it once and for all by a single dose of a drug—was definitely relinquished by Ehrlich in the salvarsan treatment of syphilis, when practical experience of this disease had brought it home to him that the largest dose of his arsenical remedies which could be exhibited without fatal consequences, failed to extirpate syphilitic infection.

Coming now to the *therapia sterilisans fractionata*, let us note with respect to the attribute *fractionata*, that this quite fallaciously suggests to the mind that the therapeutic procedure here in question proceeds upon the same lines as the procedure of fractional sterilisation employed in bacteriological laboratories in the preparation of culture media which do not support high temperatures. The fractional sterilisation which comes in that case into application depends upon the principle that microbic spores, which an application of moderate heat fails to kill, grow out when that heat is withdrawn into forms susceptible of being killed by such moderate temperatures as were initially ineffective.

Now, nothing of the sort can be supposed to supervene in the case of syphilitic spirochaetes or other microbes living parasitically in the body. Not only are these micro-organisms not converted during treatment into more vulnerable forms, but, as Ehrlich's own work and that of Morgenroth showed, parasitic microbes tend to become more resistant to whatever drug is administered.

By the establishment of this general law, Ehrlich,

in point of fact, withdraws from his *therapia sterilisans fractionata* all that scientific countenance which his nomenclature had illegitimately procured for it. And we shall presently have to inquire whether there is, in point of fact, any other scientific defence that can be adduced in defence of this seemingly unwarranted therapeutic procedure.

Finally, a few words may be said about the therapeutic procedure which employs two pharmaco-chemical agents and attacks the original microbic population with the first, and then such residue of that population as may survive with the second agent. This therapeutic device was called by Ehrlich a *cribrum therapeuticum*, for it was, as seen in his mind's eye, a device in which the physician places in position in the blood first a chemical barrier or grid so oriented as to intercept the bulk of the infecting microbes; and after that a second chemical grid oriented so as to hold back any micro-organisms which might succeed in getting past the first filter trap. As soon as we visualise this method of attack and meditate upon it, our mind sees that it can affect only microbes in the blood stream and the regions irrigated by this, and that it will leave quite unscathed those that have already penetrated into the remote backwaters.

With this we have completed our critical study of Ehrlich's terminology, and there will have been carried away from that critical analysis at least this, that the doctrine enunciated in those terms is inadequate and also in many respects erroneous. Our first task must accordingly be to try to win our way to a fuller and clearer comprehension of the problem which confronts the pharmacotherapist.

Reflection will show that we have here (and the same, of course, holds of immuno-therapy) not one but two separate problems. The one is a purely chemical problem; the other a problem in therapeutic engineering.

Let us consider, first, the one which is exclusively chemical. The task of composing a pharmaco-chemical bactericidal agent which shall be intracorporeally active is, as will be appreciated, infinitely more difficult than that of producing or finding an antiseptic of the ordinary kind. When a chemist is asked to provide the ordinary kind of antiseptic, all he is asked to do is to find a chemical agent which will destroy microbes, it being understood that the microbes shall be lying nude and exposed to chemical attack. When, on the other hand, a chemist is asked to produce a pharmaco-chemical bacterial agent which shall be intracorporeally active, there is required from him an agent which will kill this or that species of microbe not only when it is lying nude, but also when it is enveloped in albuminous fluids and secretory fluids of all kinds. And there is further required of him that he shall compose an agent which will kill microbes in the body without injuring physiological

elements which are either directly essential to life or requisite for antimicrobial defence.

And the above does not constitute by any means a full account of what is required of a pharmaco-chemical agent. Not only must such an agent be poisonous for microbes, and so far as possible non-poisonous for the organism, but it must also be rapid in action so that it may complete its task before it is eliminated or rendered inactive.

The importance of this provision will be clear when we consider that it has been ascertained with respect to optochin,¹ operating upon the pneumococcus in blood in vitro in the maximum dose admissible in treatment, and again with respect to neosalvarsan,² operating upon the streptococcus under the same conditions, that these drugs do not poison the microbes until they have been in action for a period of many hours. And in this connexion there must be taken into account also the fact that in the body pharmacotherapeutic agents are subject to rapid wastage. We know, to begin with, that the kidney and liver are continuously at work removing foreign elements from the blood, and we know, further, with respect to bactericidal drugs, that unless they have been completely purged of their affinity for albuminous substances, they are, when employed in the body, subject to a further important wastage by the fact that they tie themselves up to the albuminous elements of the blood and tissues.

Having realised how difficult it is for the chemist to produce (and, of course, we cannot reasonably expect nature to provide ready-made) effective pharmaco-chemical bactericidal agents, we may now turn to consider the further problem which confronts the physician who has to bring such agents into application, not only (for that is a comparatively simple matter) upon microbes circulating in the blood, but also (and this is what is really difficult) upon microbes dispersed throughout the organism.

It is, in point of fact, a grave blot upon Ehrlich's wonderful work upon pharmacotherapy that he failed to realise why his projected *therapia magna sterilisans* in syphilis had come to nought. He, as we saw above, attributed this to his arsenical preparations having still, after all his efforts, retained considerable toxicity. Consideration of his now universally familiar therapeutic fractional coefficient $\left(\frac{\text{dosis tolerata}}{\text{dosis efficax}}\right)$ does not, however, elucidate the failure of the *therapia magna sterilisans*. For that formula quite fails to explain why a drug which is efficacious when applied to one part of an infecting microbial population, is ineffective with respect to another part of that same population.

¹ Moore and Chesney : Archives of Internal Medicine, 1917, xxi., 659.

² Colebrook, L. : Unpublished researches.

Now, as will be shown, the real answer to this is that one part of the infective microbes are circulating in the blood or lie in regions to which there is ready access from the blood, while the other part lies in regions so physiologically remote that it might quite safely be postulated in connexion with treatment by arsenic, that even were 1000 times a lethal dose to be administered, no trace of that agent would ever penetrate there.

It will help us to realise that this is the true position of affairs if we consider for a moment the plan upon which the organism is constructed. The body is, in point of fact, constructed upon a plan of water-tight or almost water-tight compartments. Between the blood and the lymph is interposed the capillary endothelium which prevents all direct inter-penetration of fluids and permits only of interfusion by dialysis and restricted filtration. The lymph again is divided off from what we may call the *secretory fluids* by secretory membranes. How rigidly such membranes divide off the mother liquor (the lymph) from the secretory product is seen when we contrast the composition of the lymph with that of (a) the cerebro-spinal fluid; (b) the synovial fluid of the joints, bursæ, and tendons; (c) the aqueous and vitreous humour; (d) the mucus which coats the surfaces of the mucous membranes; and (e) the secretions proper, such as the tears, the saliva, the milk, the bile, and the urine.

It will be manifest from the above that the fluids of the body can, from the point of view of their accessibility to therapeutic operations, be ranged into three categories. There is, to begin with, the blood which can be directly influenced by the injection of chemical agents; then the lymph which can normally (wounds are here excluded from consideration) be reached only indirectly through the medium of the blood; and, finally, the secretory fluids which can be reached only remotely through the medium of the lymph.

Before addressing ourselves to the problem as to how chemical agents (I use the comprehensive term because the problem we are engaged upon concerns immuno-chemical as well as pharmaco-chemical agents) can be brought into operation not only in the blood, but all over the body, we must try to arrive at a clear conception as to what will happen when microbes obtain access, as the case may be, to the blood, the lymph, or the secretory fluids. And we shall do well to put to ourselves, in connexion with each category of fluid, the following three questions: *first*: Are microbes killed in this fluid by an onslaught of first intention? *Secondly*: How do such survivors as are left over after such onslaught make good their footing in the medium which has proved fatal to the majority? and *lastly*: How are such ensconced microbes subsequently combated?

We may begin by considering what happens when microbes obtain access to the blood stream. Here, except in the case where specially virulent microbes are in question, all, or at any rate a large proportion, are killed off by an onslaught of first intention, the sero-vulnerable microbes being destroyed by the torrent of bactericidal blood fluid which is brought to bear upon them, while the serophytic microbes (those which can draw nutriment from, and can accordingly grow out in the blood fluids) are, as soon as they get stranded in capillaries, phagocytosed and killed by the leucocytes. Further, when they are carried into the liver they are killed there after ingestion by endothelial cells.³

The microbes which survive this first onslaught make good their footing by rendering the blood apophylactic. They effect this (*a*) by absorbing agglutinating, opsonic, and bactericidal elements from the blood fluids, (*b*) by secreting toxins which either keep the leucocytes at bay or kill them.

Where there has been an incursion of large numbers of living microbes into the blood, and likewise where a massive dose of vaccine has been administered, the whole circulating blood may be brought down to a lower level of antibacterial, or, to speak in chemical terms, bacteriotropic potency—in other words, a general *negative phase* may be induced.

More frequently, however, the antibacterial potency of the blood will be reduced only in the immediate environment of the surviving microbes. These will, as a result of this, be lodged in non-bacteriotropic, or, as we may also call them, ecphylactic niduses. The formation of ecphylactic foci in infected tissues and organs will, as reflection will show, be dependent upon an arrest of the blood stream. So long as the circulation is maintained, the blood which has, by passing through the infected region, lost in antibacterial power will be continuously replaced by newly arriving antibacterially potent blood. When, however, the circulation is anywhere arrested, the blood will, by continued contact with the bacteria, become more and more poisoned and depleted in protective substances. And, *mutatis mutandis*, this will apply also when a portion of infected blood becomes converted into a clot, or when a quantum of non-coagulated blood is brought to a standstill by the blocking of a vessel by clot.

But intravascular clotting is very far from being the only event that will produce a local arrest of the circulation. Other physiological happenings can also bring about that result. We now know from Krogh's researches⁴ that capillary loops are intermittently shut down by muscle cells upon their walls, and again opened up. And when we reflect on what

³ Manwaring and Coe : Jour. of Immunology, 1916, i., 401. Opie : General Review, Jour. Amer. Med. Assoc., Nov. 14th, 1925.

⁴ Harvey Lectures, Series XVIII., 1922-23.

must happen when capillaries through which infected blood is passing are shut down, we realise that the microbes which are in passage may be left high and dry upon the vessel walls or be imprisoned in isolated parcels of blood left behind in the lumen of the vessels. Opportunity may in this way be provided for the elaboration of ecphylactic foci. In relation to this I have proffered by way of suggestion that typhoid spots and other bacterial skin eruptions may quite well originate in this manner. It should be borne in mind in connexion with this suggestion that comparative measurements of (a) the agglutinins of serum derived from lymph admixed with blood obtained by pricking typhoid spots, and (b) of the agglutinins of blood obtained from the finger of the typhoid patients in question, have brought out the fact that the blood fluids obtained from the bacterial rash have only a tithe of the agglutinating power of the circulating blood.⁵ And, presumably, exactly the same holds of the bactericidal power of these fluids. Further, in connexion with the development of bacterial rashes in typhoid fever and certain other septicæmias, this additional point may be considered. Microbes stranded in empty capillary loops in the dermis will probably, inasmuch as such microbes are less likely to be disturbed by a flushing out of the capillaries, find more favourable conditions for growth than would microbes stranded in capillary loops in muscles and glands. For, supposing microbes to be held back in the situations last mentioned by the closing down of capillaries, they would, when the hyperæmia which goes with muscular and glandular activity supervenes, inevitably be swept out to meet their fate in the general circulation.

In addition to the machinery which closes down the capillaries there is in the organism other machinery which brings to a standstill blood previously in circulation. It has recently been shown by Barcroft⁶ that the spleen regulates the volume of blood in circulation by loading itself up with additional blood when the volume of the circulating fluid is in excess of requirements; and by disbursing that blood when a larger volume of circulating fluid is required. It needs no gift of second sight to see that the withdrawal of blood into the stagnant diverticulum of the spleen will, in the case where that blood is infected, provide the microbes with opportunity for encasing themselves in ecphylactic envelopes. This no doubt accounts for the infecting microbe being regularly found in the spleen in typhoid fever, in Malta fever, in spirillum fever, and in anthrax; and for its being found there in large numbers (and in typhoid fever in the form of definite colonies) when the circulating blood is sterile. And again in this connexion it deserves to be remembered that in the three first-

⁵ Wright and Lamb: *THE LANCET*, Dec. 23rd, 1899.

⁶ *THE LANCET*, 1926, i., 544.

mentioned septicaemias with regard to which data are available⁷ the blood from the spleen has been found in each case conspicuously inferior in antibacterial potency to the blood from the heart.

Turning now to the question as to how microbes which have ensconced themselves in ecphyllactic niduses in the blood are subsequently combated, we may note that here both mechanical factors (in the form of alterations in the circulation), and chemical and biological factors (in the form of increased antibacterial potency of the leucocytes and blood fluids) may play their part. It will suffice in connexion with these last to note that the leucocytes which may under the stimulus of infection have acquired increased confrontation power and phagocytic efficiency; and the blood fluids, which may under that impulse have acquired increased bacteriotropic and antitryptic powers, may by degrees come into operation upon the microbes sheltering in ecphyllactic niduses. With regard to the mechanical factors, the points of importance are these: Blood-vessels which have been closed down may be opened up, the circulating blood with its superior antibacterial potency being this let in upon bacterial colonies which have grown out in ecphyllactic niduses. Further, by contractions of the spleen blood which has been lying stagnant in its diverticula may be returned to the circulation, the contained bacteria being thus resubjected to attack by the circulating blood fluids and leucocytes.

It is in this connexion interesting to ponder the question as to why in the ordinary streptococcal septicaemia there is neither growth of streptococci in colonies in the spleen, nor a bacterial eruption such as would indicate an outgrowth of microbes in the capillaries of the skin. In connexion with that problem it may be thrown out by way of suggestion that the absence of streptococcal growth in the spleen and in the cutaneous capillaries may perhaps stand in relation to the rigors. For see-saw changes in the circulatory system are of the essence of a rigor. In the cold stage the capillaries of the skin would be closed down, room being found for the expelled blood by the opening up of the diverticula in the spleen. In the hot stage the capillaries of the skin would be widely thrown open and any microbes which had been stranded there would be carried off into the circulating blood. And concurrently the spleen would contract to furnish the additional volume of blood required, and with this any microbes which had found temporary lodgment in its diverticula would in their turn be ejected into the blood stream.

We can now pass from the events which follow the introduction of microbes into the circulating

⁷ Courmont: *Comptes Rendus Soc. de Biologie*, 1897. Wright and Lamb: *loc. cit.*; Lamb: *Scientific Memoirs by Medical Officers of the Army in India*, Part XII., 1901.

blood to those that ensue when microbes are implanted into the lymph-infiltrated tissues. Two points in particular must here be borne in mind: first, that there is not normally to be found there any population of leucocytes such as could protect them against an incursion of microbes; and, secondly, that lymph which lies in the tissues would, if we may generalise from such data as are available, appear to be of less bacteriotropic, and in particular of less antitryptic, potency than the circulating blood fluids. Microbes entering the tissues will accordingly be subjected to no such immediate assault as microbes entering the blood. Nevertheless, if we look a little further and regard the fact that reinforcements of leucocytes and serous fluid can be very rapidly poured in from the blood we may (and in reality this is merely forsaking verbal accuracy for substantial truth) accredit the lymph lying in the tissues with a faculty of killing microbes by first intention.

But—and this is all important as explaining the conditions under which microbes establish themselves in the tissues—effective killing of microbes in the lymph spaces is achieved only when there is adequate transport of phylactic elements from the blood into the tissues, and further only when a proper balance is conserved between its two elements, leucocytic immigration and serous effusion.

(1) When leucocytic immigration into the focus of infection is inhibited by the agency of bacterial toxins and serous fluid containing few or no leucocytes is transported into the seat of infection, there is furnished to the invading microbes (let it be remembered that these are in practically every case serophytes) a ready-made ephyllactic nidus. To begin with, the transuded fluid provides the microbes with a favourable nutrient medium. Added to that phagocytic activity on the part of such leucocytes as are contained in the effusion is rendered impossible by the fact that leucocytes cannot dive into fluid and swim out in pursuit of microbes. And, finally, such leucocytes as have come out into the lymph cannot by reason of their paucity communicate to it any appreciable bactericidal power. This will be the position of affairs when we are dealing with œdematous swelling of the subcutaneous tissues or effusion into serous cavities.

(2) The formation of ephyllactic niduses in infected tissues will perhaps be favoured also in the case where emigration preponderates over transudation, and the emigrated leucocytes collect forming impacted foci of suppuration. In foci—such as we have in abscess sacs and in suppurating wound cavities—the leucocytes will under the influence of bacterial toxins, of deleterious external influences, or of both, first lose their power of phagocytosis and then succumb and disintegrate. When that happens the trypsin set free will reduce the

antitryptic power of the surrounding fluid ; and given that a considerable number of leucocytes disintegrate in a relatively small quantum of liquor puris, this will be converted into a definitely tryptic fluid. In the former case serophytic growth will be facilitated ; and in the second not only serophytic but also non-serophytic microbes will be lying in a medium in which they can pullulate unrestrained.

Passing now from the study of the genesis of ecphylactic foci in the tissues to inquiry as to how the organism can combat microbes which are growing in such a nidus, there have here, as in the case of the blood considered above, to be regarded, first mechanical and secondly chemical and immunological factors. In the case where an immoderate serous effusion has converted the site of infection into an ecphylactic nidus, the position (we are assuming, of course, that there is no therapeutic interference) can be retrieved by a spontaneous resorption of the excess of fluid or a supplementary emigration of leucocytes. Similarly, where a breaking down of emigrated leucocytes and a corresponding blunting off of the antitryptic reaction of the transudation fluid has converted the seat of infection into an ecphylactic focus the situation would be retrieved by the supervention of further serous effusion. For such superadded effusion would counteract leucocytic disintegration and at the same time limit serophytic, and arrest if such were in question serosaprophytic, microbic growth. Finally, it requires to be added by way of a rider that if the reinforcing leucocytes which immigrate into the focus of infection possess by virtue of an immunising response made by the organism increased confrontation power and increased phagocytic efficiency, and, similarly, if the reinforcing transudation fluid which is effused into the focus of infection has greater antibacterial potency, this improvement in the quality of the reinforcements will in each case conduce to a greater slaughter of microbes.

Having now considered how bacterial infections are combated in the blood, and in the lymph and tissues which are impregnated with lymph, our next task will be to inquire what provision exists for dealing with microbes which have found their way into a secretory fluid, or a tissue which is impregnated by or irrigated with a secretory fluid. In this inquiry a distinction must be made between three categories of secretory fluids. The first kind would be those which have the function of irrigating internal or external surfaces which lie open to infection from without. The secretory fluids which would be comprised in this class—in other words, tears, saliva, and mucus—possess the power of destroying all, other than specially acclimatised species of microbes. Let it be noted in passing that the bactericidal and bacteriolytic power here in question is a function of an antibacterial element (the so-called lysozyme)⁸

⁸ A. Fleming : Proc. Roy. Soc. B., 1922.

which is distinguishable from the antibacterial elements of the blood fluids. The second class of secretory fluids comprises the synovia of the joints, tendon-sheaths, and bursæ, further the aqueous and vitreous humour, and, lastly, the cerebro-spinal fluid. The third and last class of secretory fluids would be the secretions proper, such as the milk, the bile, and the urine. The two last specified kinds of secretory fluids possess either insignificant antibacterial power, or, in the case of the cerebro-spinal fluid, so far as is known, none at all.

Coming now to what has application to the case where microbes have invaded a secretory fluid, or a tissue which is bathed in, or a surface which is irrigated by, or a cavity which is filled with such a fluid, reflection will show that here antibacterial elements from the blood might be conveyed into the site of infection by one or other of two channels. It is *in primis* conceivable that drugs—as distinguished from antibodies—might be extracted from the lymph by the secretory epithelium and be excreted into the site of infection.

We know that urotropin passes in this way from the blood into the cerebro-spinal fluid and the urine; that methylphenolphthalein passes thus into the bile; iodides into the saliva; and various drugs into the intestinal secretions. But these are altogether exceptional occurrences, and even a moment's reflection will show that the odds against a pharmacological bacteriotropic agent or an antibody passing through an intact secretory membrane into, let us say, the tears, or the vitreous humour, or the synovial fluid, or any secretory fluid other than milk are so great as to be almost incapable of expression in figures.

Coming now to the alternative channel by which antibacterial elements contained in the blood might be transported into the secretory fluids, it will be appreciated that blood-fluids containing drugs or antibodies would in inflammation which involved a destruction of secretory epithelium be transported by way of the lymph directly into the focus of infection. Furthermore, consideration will show that antibodies from the blood might also by the agency of negative pressure be drawn out into a secretory fluid. Reference is made later to the work of Speranski,⁹ which shows in connexion with the treatment of tetanus and rabies that therapeutic substances in sera can by completely aspirating the cerebro-spinal fluid be drawn from the subdural spaces into the substance of the central nervous system. Turning to the leucocytes it is conceivable that these might, even through an intact (and a fortiori through a damaged) secretory membrane emigrate into a secretory fluid.

But with regard to all such direct transport of

⁹ Speranski: *Annales de l'Institut Pasteur*, xli., February, 1927.

protective elements from the blood into secretory fluids the following requires to be specially emphasised. The blood fluids will always work at a great disadvantage when they are either diluted or frequently washed away by secretory fluids. And similarly leucocytes emerging into a secretory fluid will be eminently ineffective. Illustration of this is furnished by, for example, gonorrhœal infections of the conjunctiva, genital mucous membrane, and joints.

The foregoing will have made clear that the efficacy of antibacterial treatment by pharmaco-chemical bacteriotropic agents depends not only upon their entering into rapid destructive chemical combination with the microbes and exclusively with these, but also upon the chemical agents in question being transported from the blood into the lymph and from the lymph into the secretory fluids. It has further appeared that the failures of pharmaco-chemical—and the same holds good of immuno-chemical treatment—are, as it would seem, more often imputable to a default of convection than to a default in the chemical constitution of the therapeutic agent employed.

And the mental picture we have just arrived at will be seen to fit in well with clinical observation which teaches that antibacterial treatment is wont to be more effective early in an infection—that is, when the microbes still lie open to attack in the lymph and the circulating blood—than in the later phase when they have entrenched themselves in ecphyllactic foci. We have in the domain of pharmacotherapy illustration of this in the fact that salvarsan when given early in syphilis does in many cases extinguish the infection while, when given later, it very often fails to effect this. Further striking illustration of the therapeutic principle here in question is furnished by the fact that bismuth¹⁰ given to animals inoculated with the spirochætes of hæmorrhagic icterus will, if employed soon after the inoculation, extinguish the infection, while it fails to do this when given after the lapse of a few days. This is the exact reverse of what happens with sanocrysin. The experiments of my fellow-worker, R. M. Fry,¹¹ have shown that this agent, which was reputed to enter into destructive chemical combination with tubercle bacilli, does not, even when employed in concentrations much stronger than would be possible in the body, interfere with the growing out of tubercle bacilli into colonies in the blood *in vitro*. And further, the experiments of Madsen and Morch¹² have shown: *first*, that sanocrysin does not, when given with or immediately after an injection of tubercle bacilli in any way hinder the march of the infection; and, *secondly*, that the drug given at a later date, and employed in

¹⁰ Sazerac, Nakamura, and Kitcheritz: *Comptes Rendus Acad. des Sciences*, 1927, 184, 411.

¹¹ *British Journal of Exp. Pathology*, 1926, vii., 174.

¹² Madsen and Morch: *Acta Tuberculosa Scandinavica*, 1926, ii., 99.

strictly adjusted doses, saves a certain number of animals. The former of these findings is in obvious accord with the results obtained by Fry. The latter is, no doubt, explained by the fact that sanocrysin induces, like tuberculin, an infractive inflammation of ecphylactic niduses—such infraction being followed in non-resistant men and animals by a disastrous tubercular septicæmia, but no doubt in men and animals whose blood has been fortified by auto-immunisation,¹³ by a destruction of the tubercle bacilli carried into the circulation.

The general principles which should inform all antibacterial treatment having now been set forth, our next task must be to consider the method by which antibacterial elements which may be present in the circulating blood can be brought into operation upon infecting microbes in ecphylactic niduses.

We may conveniently begin our consideration of these methods by considering what we here require by way of terminology. We require, first, a general term which will embrace every kind of procedure which brings destructive agencies into operation upon microbes which would in the natural course of events escape unscathed. The term *kataphylaxis* will, perhaps, supply what is here wanted. We may further desire to distinguish *kataphylactic procedures* into: (a) *leucocytagogic procedures* which bring leucocytes, and (b) *seragogic procedures* which bring serum into operation. And, finally, where we have in mind the bringing of pharmaco-chemical elements into operation in regions which are sequestered from the blood stream, we may employ a term which is already in use, the term *kataphoresis*.

We may now take up the study of the methods of bringing pharmaco- or immuno-chemical substances into operation upon microbes which have elaborated ecphylactic niduses for themselves within the domain of the vascular system.

We have seen that opportunity for the establishment of ecphylactic niduses within the domain of the vascular system is provided, *first*, when the blood current is arrested by intravascular coagulation; *secondly*, when capillaries in the skin or elsewhere are closed down by the contraction of muscle cells in their walls; and *thirdly*, when blood which has been in circulation is brought to rest in the diverticula of the spleen. In the first case all that can be done is to administer citric acid¹⁴ with a view to diminishing blood coagulability and preventing the reinforcement of the primary clot by a series of supplementary

¹³ Wright: Paper on the Cultivation of the Tubercle Bacillus in the Blood, THE LANCET, 1924, i., 218.

¹⁴ Wright: B.M.J., July 14th, 1894. Wright and Knapp: Causation and Treatment of Thrombosis Occurring in Connexion with Typhoid Fever, THE LANCET, 1902, ii., 1531.

clottings.¹⁵ When by timely intervention those reinforcements of the clot have been warded off, the lumen of the vessel will be rendered patent by the normal retraction of the fibrin and the washing out of the red corpuscles which constitute what we might call the "stuffing" of the clot. It will be obvious that when this packing of red corpuscles has been removed dissolved antibacterial elements both chemotherapeutic substances or antibodies, and also efficient leucocytes—supposing always that we have these in the circulating blood—will come into operation upon the microbes which have been sheltering within or behind the clot.

In the case where microbic colonies are lodged in the capillaries of the skin, these can be opened up by heat and other vasodilator influences. And such opening up will, in the case where antibacterial substances are circulating in the blood, result in these being let in upon the microbic colonies, while the bulk of the microbes will be swept out into the circulating blood and will, when that blood is bactericidally potent, be destroyed there. Let us call this *infractive and korethric* treatment (*korethric* from *korethros*—a besom or sweeping brush).

Ecphylectic niduses in the spleen require, like those in the capillaries, *korethric* treatment. But here instead of producing dilatation we require to produce contraction of the spleen. We might here avail ourselves of the fact brought out by Barcroft that vascular changes which call for an increased volume of circulating blood (changes such as general cutaneous vasodilatation and the dilatation which accompanies muscular action) produce a reflex contraction of the spleen. Or again, we might, making use of other physiological data furnished by Barcroft, produce a reflex contraction of the spleen by cutting down the respiratory value of the blood by administering carbonic oxide, or better (for this will be innocuous) ordinary carbonic acid gas. And, lastly, we might employ adrenalin, or again certain other pharmacological substances studied by Binet, Cardot, and Fournier¹⁶ and so produce direct in lieu of reflex contraction of the spleen.

It is interesting to note in connexion with the exhibition of adrenalin that it has in cases of latent malaria been successfully employed for contracting the spleen and evacuating into the circulating blood (for purposes of diagnosis) crescents and other malarial parasites which have, as the common formula says, "retired from the superficial circulation into the spleen." It will be recognised that the parasites in question are not, in point of fact, organisms which have "retired" into the spleen, but organisms which (and the same happens to typhoid bacilli in typhoid

¹⁵ Wright and Colebrook: *Technique of the Teat and Capillary Tube*, Chart VII., Appendix 1, pp. 133, et seq.

¹⁶ *Comptes Rendus Soc. de Biologie*, 1927.

fever, and spirilla in relapsing fever) have been able to establish favourable conditions for growth in the stagnant blood of the spleen, when those organisms which continued to circulate in the blood were killed.

A further point of interest in connexion with the administration of adrenalin in these cases is that very severe attacks of malaria are reported to have been produced by the treatment.

We have here again illustration of the fact that it is a sinister procedure to sweep microbes out from the foci in which they are lying quiet into the general circulation, unless we have ascertained before we do so that the blood in the general circulation has become bactericidally potent, or unless antibodies or pharmaco-therapeutic remedies have been introduced into the blood in order to prevent a generalisation of the infection. The risk of disseminating microbes into blood not capable of killing them was long ago abundantly illustrated in connexion with Koch's treatment of phthisis by tuberculin. It has also recently been illustrated in connexion with the administration of sanocrysin to tuberculous patients.

We pass now to consider the kataphylactic procedures which can be brought into application upon ecphylectic foci situated in lymph-infiltrated tissues and secretory fluids. Let us distinguish these into procedures which are both leucocytagogic and seragogic, and into those which are seragogic only.

<i>Procedure.</i>	<i>Physiological action.</i>
(1) Induction of active hyperæmia and inflammatory irritation.	Leucocytagogic and seragogic.
(2) Induction of passive congestion by Bier's bandages.	Seragogic only.
(3) Induction of œdema ex vacuo by depletion and evacuation of the local focus of infection.	Seragogic, and possibly leucocytagogic.
(4) Lowering of the general blood coagulability.	Seragogic only.
(5) Induction of Arthusian inflammation.	Leucocytagogic and seragogic.
(6) Employment of albumino-tractor (intertracting) agents.	Seragogic only.

The principles of the first three of these procedures and the methods of exploiting them being, it may be assumed, universally familiar, it will be unnecessary to say anything about them here, except only again to refer to the brilliant work of Speranski,¹⁷ which shows in connexion with the treatment of rabies and tetanus (and the same would probably apply to all other cerebral infections) that antimicrobial and antitoxic elements contained in sera introduced into the subdural space can by the agency of negative pressure (established by the complete evacuation of the cerebro-spinal fluid under anæsthesia) be drawn into the substance of the central nervous system.

¹⁷ Loc cit.

With regard to the principles of the three last katalytic procedures these may with advantage be briefly elucidated.

Lowering of the General Blood Coagulability.—I showed in a series of papers now many years ago that urticaria, chilblains, physiological albuminuria, and anasarca could all be brought under the general heading of serous hæmorrhage, and that such serous hæmorrhage, or to give it its more usual name, excessive serous effusion, is correlated with diminished blood coagulability and is aggravated by the exhibition of citric acid and other agents which reduce blood coagulability, and alleviated by calcium chloride and other agents which increase blood coagulability.¹⁸ Consideration will show that the principle here involved has application also to the treatment of bacterial infection in the tissues and more specially to pharmacotherapeutic treatment. For manifestly there will be better prospect of bringing a drug into operation in the tissues if the blood at the time the drug is introduced is in a state to furnish a maximum of serous exudate.

It will be interesting in this connexion to hark back to the paradox encountered earlier in this paper, the paradox that syphilitic infection is not infrequently successfully extinguished by following out that theoretically unsound procedure which Ehrlich called a *therapia sterilisans fractionata*. Let us see whether this problem can now be cleared up. Partial illumination may perhaps come to us when we reflect that a drug taken in repeated doses will, according as different tissues and different portions of the body happen, after the incorporation of the dose to be thrown into activity, be determined each time to a different anatomical region. And on the doctrine of chance there will in the case where many doses are administered be a prospect of the drug being carried in turn into all such foci of infection as are accessible. From this clinical advantage is naturally to be expected. But there is superadded to this factor of chance another physiological factor which is operating steadily, in the direction of making the sequent doses of salvarsan more and more effective. Salvarsan, given in repeated doses, regularly and markedly lowers the coagulability of the blood.

¹⁸ Wright : Remarks on Methods of Increasing and Diminishing the Coagulability of the Blood, with special reference to their therapeutic employment, *Brit. Med. Jour.*, July 14th, 1894. *Idem* : On the Treatment of the Hæmorrhages and Urticarias which are Associated with Deficient Blood Coagulability, *THE LANCET*, Jan. 18th, 1896. *Idem* : On Two Cases of Urticaria Treated by the Administration of Calcium Chloride, *Brit. Jour. of Dermatology*, vol. viii., 1896. *Idem* : On the Association of Serous Hæmorrhages with Conditions of Defective Blood Coagulability, *THE LANCET*, Sept. 19th, 1896. *Idem* : On the Pathology and Treatment of Chilblains, *THE LANCET*, Jan. 30th, 1897. *Idem with Ross* : On the Pathology and Treatment of Physiological Albuminuria, *THE LANCET*, Oct. 21st, 1905.

One can immediately see that this is bound to promote a freer flow of arsenic-carrying lymph through the tissues.

Now, if it is this—and it may well be this—that renders the theoretically unsound *therapia sterilisans fractionata* practically effective, it would be well to consider whether it would not be more rational

Photographs of Vertical and Horizontal Intertraction.

FIG. 1.

FIG. 2.

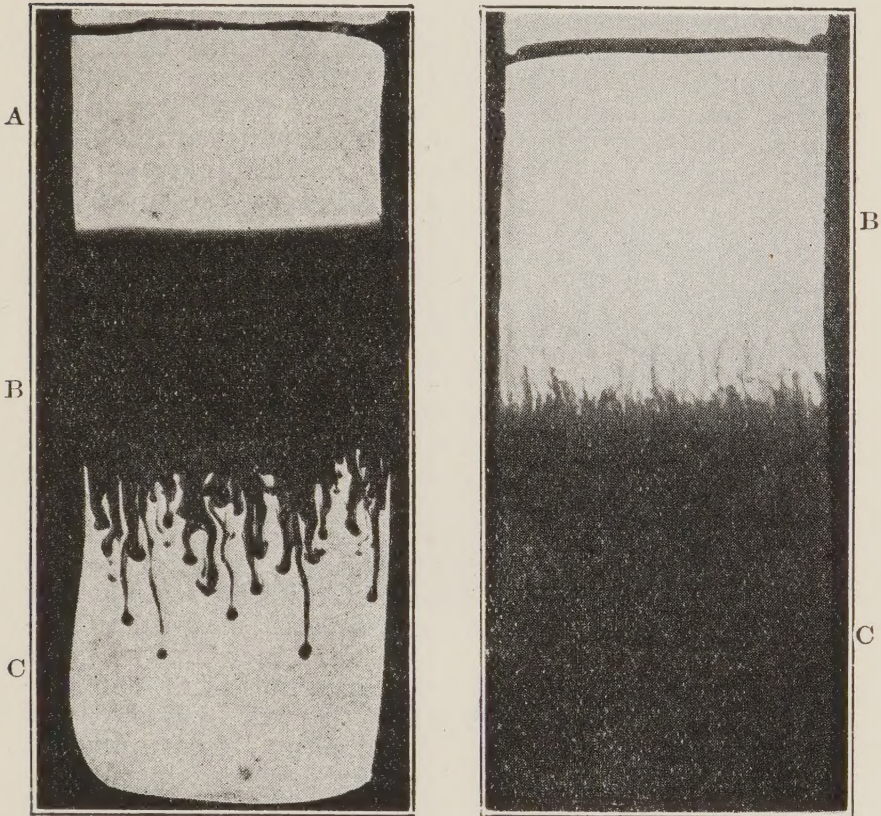


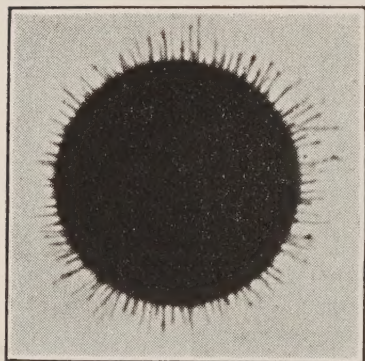
FIG. 1.—Here a layer of serum coloured with eosin (B) has been superimposed upon a layer of a specifically heavier (10 per cent.) salt solution (C). Beginning almost instantaneously the serum is rapidly drawn down (*descending intertraction*) into the salt solution in the form of pseudopodial streamers. Above the layer of coloured serum (B) the vessel is filled with water (A). Into this after long waiting the serum gradually diffuses spreading upwards not in streamers but in the form of a level horizontally dispersed wavefront.

FIG. 2.—Here uncoloured serum (B) is superposed upon a layer of coloured 10 per cent. salt solution. (C) After the lapse of a few minutes the salt solution is drawn up into the serum (*ascending intertraction*) again in the form of polypoid streamers.

to begin the treatment of syphilis by administering citric acid in quantity sufficient to diminish blood coagulability and increase with this serous effusion all over the body. One might then hope to accomplish as much by a first dose of salvarsan as is by the ordinary procedure accomplished after a long series of doses.

Induction of Arthusian Inflammation.—It was shown by Arthus¹⁹—and our understanding of the subject has been much extended by Opie²⁰—that when repeated doses of a foreign serum are hypodermically or intradermally inoculated, the third or fourth of the series (the first two having no visible effect) will be followed by some local oedema, the fifth and sixth by a more pronounced oedema, and the later injections not only by serous effusion but also by emigration of leucocytes and often by localised necrosis. It has been shown that the development of these phenomena is correlated with an elaboration of precipitins in the blood of the injected animal, and that the inflammatory reaction which follows incorporation of the foreign serum is probably due to its precipitation at the site of injection. An Arthusian reaction, quite similar to that obtained in the manner just

FIG. 3.



Here a disc of filter paper which has been fastened by a pellet of plasticine to the surface of a paraffin-rimmed cover-glass and has been impregnated with coloured serum has, after firm blotting, been floated inverted upon a 4 per cent. salt solution. Into this the serum is drawn out from the filter paper in the form of an ever-lengthening system of streamers.

contains sparse leucocytes and is itself favourable to the growth of serophytes, an Arthusian inflammation furnishes a serous effusion which may contain copious leucocytes and is (it has presumably become so probably by virtue of a liberation of bactericidins from leucocytes) definitely bactericidal. Consideration will show that this method may in the future be found to have therapeutic applications. A mixture of serum and antiserum, or possibly an antihuman precipitating serum by itself, is the sort

described, can be produced by injecting into the blood of the animal which is to receive local inoculation of a foreign serum an anti-serum to this. And again—and this is a procedure which might perhaps be employed in treating a localised infection—an Arthusian inflammation can be produced also by injecting a foreign serum admixed with precipitating anti-serum. Let us note—for the fact may have therapeutic significance—that in all varieties of Arthusian inflammation the products of inflammation differ in a respect which may render them more effective than those furnished in ordinary inflammation. While ordinary inflammation furnishes a serous effusion which

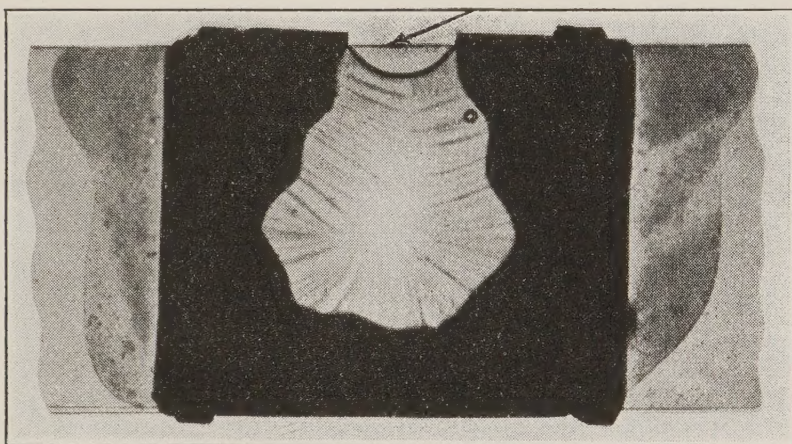
¹⁹ Comptes Rendus Soc. de Biol., 1903, p. 817. Ibid., 1478.

²⁰ Tubercle, October, 1925. Journal of Immunology, vol. ix. No. 4, 1924. Journal of Exp. Med., 1924.

of agent which could be injected not only into an infected tissue or a neoplasm, but also into an infected serous effusion or secretory fluid. I have specially in view infections of the central nervous system and not alone syphilitic infections, but others like encephalitis lethargica, infantile paralysis, and rabies.

Employment of Albumino-tractor (Intertracting) Agents. It was long ago shown by Heidenhain that strong solutions of sodium chloride and other salts and also of sugar functioned when introduced into the blood as powerful lymphagogues. In connexion with these same solutions, I have, from 1900 onwards, and in particular during the war, been pointing out that they, when introduced into wounds or sinuses,

FIG. 4.



Here a piece of specially dense filter paper has been cut out in such a way as to represent an axial section of a wound cavity. The artificial wound section thus obtained is then impregnated with coloured serum. It is then interpolated between a couple of microscopic slides and these are clamped together. This done any serum which may have escaped into the cavity is carefully evacuated, and the cavity is then filled with an ordinary 5 per cent. salt solution, or better with serum containing 5 per cent. of salt. As soon as this has been done the coloured serum is drawn out in streams from the encasing walls into the saline solution occupying the cavity of the artificial wound.

operate as powerful local lymphagogues causing a welling up of serum, and with this a cleansing of these niduses of infection from all but serophytic microbes. Further, I have recently shown²¹ that when serum and hypertonic salt solutions are brought together in vitro the two fluids are rapidly drawn the one into the other in a pattern of polypoid streamers. I have called the force which here operates and which draws the fluids the one into the other and mixes them *intertraction*. The mutual indraught of the fluids here in question can be rendered manifest to the eye by floating artificially coloured serum

²¹ Wright: Proceedings of the Royal Society B., vol. xcii., 1921; A, vol. cxii., 1926; A, vol. cxiv., 1927.

upon a 5 per cent. solution of sodium chloride in a cell which has plane walls, or alternatively by floating uncoloured serum upon coloured hypertonic salt solution in such a cell. As soon as this has been done vertical intertraction, as represented in Figs. 1 and 2, begins to manifest itself in the form of rapid and complete interpenetration of the fluids.

Horizontal intertraction can be obtained by floating upon a 4 per cent. salt solution a disc of filter paper fixed upon the lower surface of a paraffined rimmed cover-glass, and then impregnated with coloured serum. This gives appearances such as are depicted in Fig. 3.

A further experiment which illustrates the intertraction which is produced by the introduction of hypertonic salt solution into wounds is illustrated in Fig. 4. Here a dense filter paper which has been cut to represent the profile of a wound in section has been soaked in coloured serum and has been interposed between two slides. These arrangements made, the slides are clamped together, any superfluous serum in the cavity of what we may call the artificial wound is removed, and then there is filled into that cavity either hypertonic salt solution or better serum which contains 5 per cent. of salt. This done, the coloured serum which impregnates the paper is seen to flow out in the form of streamers in the wound cavity.

Consideration will show that hypertonic salt solutions can find useful kataphylactic application not only as local seragogues directly introduced into the wound for cleansing it from non-serophytic infection, but also when they are injected into the blood. They will then, as Heidenhain's classical experiments showed, function as powerful general seragogues. And thus employed they will, in the case where the circulating blood contains chemotherapeutic elements (immuno- as well as pharmacotherapeutic elements) be bound to carry these in a rapid stream through the tissues, achieving very rapidly that transport of antibacterial elements into the foci of infection which will, even when it is favoured by reduced blood coagulability, be accomplished only very slowly.

In concluding, I may, perhaps, venture to explain that acknowledgments of indebtedness to the Medical Research Council are here, for two reasons, withheld. The one is that I am doubtful of the propriety of research workers who are paid out of public funds expressing indebtedness to the agency which distributes those funds. And acknowledgments other than strictly financial ones seem here to be barred, because they might be taken to mean that the Medical Research Council (and the powers that stand behind them) desire to promote, or even look favourably upon, research work of the type embodied in this paper.